APPENDIX A

CURRICULUM VITAE
Michael Alexander Cowley

Personal Details

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Date of birth: 3rd September 1968

Nationality: Australian, I am a permanent resident of the USA.

Scientific goals: To characterize the cellular and molecular neuroendocrine mechanisms that regulate energy homeostasis in mammals, and to develop new therapeutics to modify energy balance.

Experience

Academic

2003- now — DIRECTOR of ONPRC Electrophysiology Core
Dec 2001- now — & ASSISTANT SCIENTIST, Division of Neuroscience, Oregon National Primate Research Center, Oregon Health and Science University, Beaverton, USA

ASSISTANT PROFESSOR, Physiology and Pharmacology, OHSU

My research includes electrophysiological studies of rat and mouse brain slices and cultured cells. The lab analyses receptor specific effects upon identified neurons in the energy homeostasis pathways. We are determining the mechanism and site of effect of in the brain of hormonal signals of energy status in rats, mice, genetic mutant mice, and drug treated or obese mice. Additionally we perform calcium imaging, immunohistochemistry, confocal microscopy and three-dimensional reconstructions of neuronal cytoarchitecture and *in vivo* pharmacology studies. The lab also run complex *in vivo* studies on energy balance in monkeys.

Sept. 2000 – Dec2001 — RESEARCH ASSISTANT PROFESSOR, The Vollum Institute, OHSU.

April '98 - August '00 — POST-DOCTORAL FELLOW in the laboratory of Dr. Roger D. Cone, The Vollum Institute, OHSU, Portland, OR, USA

1994- 1998 — As a GRADUATE STUDENT I designed and performed several experiments involving mRNA extraction and Northern analysis, animal surgery (ovariectomy, hypothalamo-hypophyseal disconnection and neuronal cannulations), preparation and electrophysiological assays of primary cultures of pituitary cells, Western blotting and enzyme activity assays and the development of several radioimmunoassays.

Industrial

Sept 2002 — Co-founder and Chief Scientific Officer of Orexigen Therapeutics Inc., a neuroscience company focussed on the development of obesity pharmacotherapies. Now running Phase III clinical trials. Completed successful C funding round.

Sept '02 - Sept '06 — Co-inventor on multiple patent applications around obesity drug screens and drug targets.

May '00 - May '02 — Consultant to Neurocrine Biosciences, Inc., San Diego, CA. I provided advice on "neuroendocrine control of feeding and metabolism and melanocortin neurophysiology".

Awards

•2006 – 2008	Sponsored research Award from Orexigen Therapeutics, Inc.
•2005	Award from Novo Nordisk, Denmark. Drug effects on food intake in non human primates
•2005	Supplement to Electrophysiological effects of drug combinations, Orexigen Therapeutics Inc.
•2004 - 2005	NIH supplement: NPY feeding circuits during development
•2004 - 2005	NIH supplement: Characterization of engineered mouse models of obesity
•2003 - 2008	Serotonergic mechanisms in obesity Subcontract.
•2004 - 2005	Sponsored research Award from 7TM Pharma, Denmark
•2003 - 2006	Sponsored research Award "Electrophysiological testing of drug combinations" from Orexigen Therapeutics, Inc.
•2002 - 2007	R01-DK62202- Mechanism of neuronal regulation by leptin and insulin.
•2002 - 2003	ONPRC Pilot Award. Long term effects of $PYY_{3\text{-}36}$ on macaque energy homeostasis.
•2002 - 2003	Medical Research Foundation of Oregon. Effects of obesity on neuropeptide secretion from isolated hypothalami.
•2002 - 2004	The effects of maternal obesity and high fat diet on body weight management in the offspring in the nonhuman primate. Pilot feasibility study, ONPRC. Co Principal Investigator.
•1994 - 1999	Australian Postgraduate Award, for the duration of my Ph.D. candidature
•1996	Queen Elizabeth II Silver Jubilee Trust for Young Australians, "Queen's Trust Achiever Award." To travel to the Brain Metabolism Unit in Edinburgh (U.K.) and work for several months, and later attend the 1997 US Endocrine Society annual scientific meeting, in Minneapolis, Minnesota.
•1996	Queen Elizabeth II Silver Jubilee Trust for Young Australians "Future Perspectives Forum: Personal Responsibility for Australia's Future." Trinity College, The University of Melbourne.
•1996	Endocrine Society of Australia Travel Award, to attend The 10th International Congress of Endocrinology in San Francisco.

Memberships

•	Member of the Society for Neuroscience, The Endocrine Society, the American Diabetes Association, Society for the Study of Ingestive Behavior, and The Obesity Society
•2007	Senior Editor Neuroendocrinology. Member of the editorial board of Endocrinology, Member of the Editorial Board American Journal of Physiology, Member of SSIB program committee.
•2002	Member of the editorial board of *Obesity Research*
•2002	Member of the executive committee of OHSU's Neuroscience Graduate Program
•1995 - 1996	Board of the Faculty of Medicine, Monash University, Clayton, Australia
•1994 - 1996	Vice President, then President of Prince Henry's Institute Research Students' Society

Mentoring

Post-doctoral fellows
Pablo Enriori Ph.D., Chun Xu Ph.D., Puspha Sinnayah Ph.D.
Erin Jobst PT, Ph.D., now Assistant Professor, Pacific University of Oregon
Graduate Students
Sonja Billes BS.
Co-mentoring
Rachel Batterham M.D., Ph.D., Lora Heisler, Ph.D. Both now in faculty positions in the UK.

Education

Postgraduate

1999 Doctor of Philosophy
Faculty of Medicine, Prince Henry's Institute of Medical Research, Monash University, Clayton, Victoria, Australia.
Thesis title: Subcellular mechanisms in gonadotrophs that are involved in the feedback regulation of Luteinising Hormone secretion by Oestrogen.
Supervisor: Professor Iain J. Clarke.

1993 Bachelor of Science (Honours)
Department of Physiology, Monash University, Clayton, Victoria, Australia.
Thesis title: "Reproductive Control of Foxes"
Supervisor: Professor Roger V. Short
Grade: First Class Honours.

Undergraduate

1989 Bachelor of Science,
The University of Melbourne, Parkville, Victoria, Australia.
Major study areas included Biochemistry and Psychology.

Referees

Sergio R. Ojeda
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Publications

Peer Reviewed

Munzberg H, Jobst EE, Bates SH, Jones J, Villanueva E, Leshan R, Bjornholm M, Elmquist J, Sleeman M, Cowley MA, Myers MG Jr. Appropriate inhibition of orexigenic hypothalamic arcuate nucleus neurons independently of leptin receptor/STAT3 signaling. 2007. *J Neurosci.* 27:69-74

Greenway, F.L., Martin, C.K., Gupta, A.K., Cruickshank, S., Whitehouse, J., DeYoung, L., Kamdar, K., Caruso, M.K., Roberts, A.T., England, M., Dumas, K., Floy Laidlaw, B.J., Rogers, B., and Cowley, M.A. Using intranasal lidocaine to reduce food intake. (*International Journal of Obesity*, in press).

Billes, S.K. and Cowley, M.A. Inhibition of dopamine and norepinephrine reuptake produces additive effects on energy balance in lean and obese mice. (*Neuropsychopharmacology*, in press).

Guo Y, Ma L, Enriori PJ, Koska J, Brookshire T, Cowley MA, Salbe AD, DelParigi A, Tataranni PA. Physiological Evidence for the Involvement of Polypeptide YY in the Regulation of Energy Homeostasis in Humans. 2006. *Obesity Research*. **14**:1562-70.

Reinehr T, Enriori PJ, Cowley MA, Roth CL. Pancreatic polypeptide before and after weight loss in obese children. 2006. *International Journal of Obesity*. **30**:1476-81.

Heisler LK., Jobst EE., Sutton G, Balthasar N, Zhou L, Borok E, Thornton-Jones Z, Liu HY,. Zigman JM, Kishi T, Lee CE., Aschkenasi CJ., Zhang C-Y, Yu J, Boss O, Mountjoy KG.,. Clifton PG, Lowell BB, Friedman J, Horvath TL, Butler AA, Elmquist JK.,. and Cowley MA. 2006 Serotonin Reciprocally Regulates Melanocortin Neurons to Modulate Food Intake. *Neuron*. **51**: 239-249

Dhillon, H., Zigman, J.M., Ye, C., Lee, C.E., McGovern, R.A., Tang, V., Kenny, C.D., Christiansen, L.M., White, R.D., Edelstein, E.A., Coppari, R., Balthasar, N., Cowley, M.A., Chua, S., Elmquist, J.K., and Lowell, B.B. 2006. Leptin directly activates SF1 neurons in the ventromedial hypothalamus and this action by leptin is required for normal body weight homeostasis. *Neuron*.**49**:191-206

Roth CL, Enriori PJ, Harz K, Woelfle J, Cowley MA, Reinehr T. (2005). Peptide YY is a regulator of energy homeostasis in obese children before and after weight loss. *J Clin Endocrinol Metab*.;**90**: 6386-91.

Koegler F.H., Enriori P.J., Billes S.K., Takahashi D.L., Martin M.S., Clark R.L., Evans A.E., Grove K.L., Cameron J.L., and Cowley M.A. (2005) $PYY_{(3-36)}$ inhibits morning, but not evening, food intake and decreases body weight in rhesus macaques. *Diabetes*, **54**: 3198-204..

Zhou, L., Williams, T., Lachey, J.L., Kishi, T., Cowley, M.A., and Heisler, L.K. (2005) Serotonergic pathways converge upon central melanocortin systems to regulate energy balance. *Peptides*, 26: 1728-1732.

Batterham, R. L., Cowley, M. A., Small, C. J., Herzog, H., Cohen, M. A., Dakin, C. L., Wren, A. M., Brynes, A. E., Low, M. J., Ghatei, M. A., Cone, R. D., and Bloom, S. R. (2004). Physiology Does gut hormone PYY3-36 decrease food intake in rodents? (reply). *Nature 430*.

Cowley M.A., Diano S., Tschöp M., Pronchuk N., Strasburger C.J., Bidlingmaier M., Esterman M., Smith R.G., Heiman M.L., Garia-Segura L.M., Nilni E.A., Mendez P., Low M.J., Colmers W.F., Cone R.D., Horvath T.L. (2003) The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasiss. *Neuron* **37**:649-61.

Horvath, T.L., Diano, S., Leranth, C., Garcia-Segura, L.M., Cowley, M.A., Shanabrough, M., Elsworth, J.D., Sotonyi, P., Roth, R.H., Dietrich, E.H., Matthews, R.T., Barnstable, C.J. and Redmond, D.E., Jr., (2003) Coenzyme Q induces nigral mitochondrial uncoupling and prevents dopamine cell loss in a primate model of Parkinson's disease. *Endocrinology* **144**:2757-2760.

Cowley, M.A.; Batterham, R.L.; Small, C.J.; Herzog, H.; Cohen, M.A.; Dakin, C.L.; Wren, A.M.; Brynes, A.E.; Low, M.J.; Ghatei, M.A.; Cone, R.D.; Bloom, S.R. (2002) Gut hormone PYY(3-36) physiologically inhibits food intake. *Nature* **418**:650-4.

Heisler, L.K., Cowley, M.A., Tecott, L.H., Fan, W., Low, M.J., Smart, J.L., Rubinstein, M., Tatro, J.B., Holstege, H., Lee, C.E., Cone, R.D., Elmquist J.K. (2002) Fenfluramine Activates Central Melanocortin Pathways. *Science* **297**:609-611.

Cowley, M.A., Smart, J.L., Rubinstein, M., Cerdán, M.G., Horvath, T.L., Diano, S., Cone, R. D., Low, M.J. (2001) Leptin activates anorexigenic POMC neurons through a neural network in arcuate nucleus. *Nature* **411**:480-484.

Campbell, R.E., ffrench-Mullen J.M.H., Cowley M.A., Smith M.S., Grove, K.L. (2001). Hypothalamic circuitry of neuropeptide Y regulation of neuroendocrine function and food intake via the Y5 receptor subtype. *Neuroendocrinology* **74**: 106-119.

Grove, K.L., Campbell, R.E., ffrench-Mullen J.M.H., Cowley M.A., Smith M.S. (2000). Neuropeptide Y Y5 receptor protein in the cortical/limbic system and brainstem of the rat: Expression on gamma-aminobutyric acid and corticotropin releasing hormone neurons. *Neuroscience* **100**:731-740.

Cowley, M.A., Pronchuk, N., Fan, W., Dinulescu, D.M., Colmers, W.F., Cone, R.D. (1999). Integration of NPY, AGRP, and melanocortin signals in the paraventricular nucleus of the hypothalamus: Evidence of a cellular basis for the adipostat. *Neuron* **24**:155-163.

Cowley, M.A., Chen, C., Clarke, I.J. (1999). Estrogen transiently increases delayed-rectifier, voltage-dependent potassium currents in ovine gonadotropes. *Neuroendocrinology* 69:254-260.

Cowley, M.A., Rao, A., Wright, P.J., Illing, N., Millar, R.P., Clarke, I.J. (1998). Evidence for differential regulation of multiple transcripts of the gonadotropin releasing hormone receptor in the ovine pituitary gland; effect of estrogen. *Molecular and Cellular Endocrinology* **146**:141-149.

Lew, R.A., Cowley., M. A., Clarke, I.J., Smith, A.I. (1997). Peptidases that degrade gonadotropin-releasing hormone: influence on LH secretion in the ewe. *Journal of Neuroendocrinology* 9:707-712.

Thom, B., Canny, B.J., Cowley, M.A., Wright, P.J., Clarke, I.J. (1996). Changes in the binding characteristics of the μ, δ and κ subtypes of the opioid receptor in the hypothalamus of the normal cyclic ewe following treatment with ovarian steroids. *Journal of Endocrinology* **149**:509-518.

Chapters and Reviews

Cowley MA, Grove KL. To be or NUCB2, is nesfatin the answer? 2006. Cell Metab. 6:421-2.

Enriori PJ, Evans AE, Sinnayah P, Cowley MA. Leptin resistance and obesity. 2006.. *Obesity Research*:**14** Suppl 5:254S-258S.

Jobst EE, Enriori PJ, Sinnayah P, Cowley MA. Hypothalamic regulatory pathways and potential obesity treatment targets. 2006. *Endocrine*. **1**:33-48.

Koegler, F.H. and Cowley, M.A. (2005) Practical Approaches to Pharmacological Studies in Nonhuman Primates. *In* "The Handbook of Experimental Animals, The Laboratory Primate", pp. 437-447. Elsevier Academic Press, San Diego, CA. S. Wolfe-Coote, Ed.

Batterham, R.L. and Cowley, M.A. (2005) Endocrinology of Fat, Metabolism, and Appetite. *In* "Endocrinology: Basic and Clinical Principles", 2nd Edition, pp. 375-390. Humana Press, Totowa, NJ. S. Melmed and P.M. Conn, Eds.

Grove, KL & Cowley MA. (2005). Is ghrelin a signal for the development of metabolic and reproductive systems? *J Clin Invest.* **115**: 3393-7.

Jobst, E.E., Enriori, P.J., and Cowley, M.A. (2004) The electrophysiology of feeding circuits. *Trends Endocrinol. Metab.* **15**:488-499.

Cowley M.A. and Grove K.L. (2004) Ghrelin—Satisfying a hunger for the mechanism. *Endocrinology* **145**(6):2604-2606.

Dobbins, R.L., Cowley, M.A., and Foster, D.W. (2004) Glucose, Lipid and Protein Metabolism. *In* "Textbook of Endocrine Physiology", pp. 377-406. Oxford University Press, New York, NY. J.E. Griffin & S.R. Ojeda, Eds.

Cowley, M.A., Cone, R.D., Enriori, P., Louiselle, I., Williams, S.M. and Evans, A.E. (2003) Electrophysiological actions of peripheral hormones on melanocortin neurons, *Ann NY Acad Sci* **994**:175-186.

Cowley, M.A. (2003). Hypothalamic melanocortin neurons integrate signals of energy state. *European Journal of Pharmacology*, **480**:3-11.

Heisler, L.K., Cowley, M.A., Kishi, T., Tecott, L.H., Fan, W., Low, M.J., Smart, J.L., Rubinstein, M., Tatro, J.B., Zigman, J.M., Cone, R.D. and Elmquist, J.K. (2003) Central serotonin and melanocortin pathways regulating energy homeostasis, *Ann N Y Acad Sci* **994**:169-174.

Cone, R.D., Cowley, M.A., Butler, A.A., Fan, W., Marks, D. L., and Low, M.J. (2001) The arcuate nucleus as a conduit for diverse signals relevant to energy homeostasis. *Int J Obes Relat Metab Disord.* **25** Suppl 5:S63-S67.

Invited Talks

"Cellular Basis for Leptin Resistance, and Ways to Bypass it". NGP Faculty Address, Oregon, September 2006

"Leptin resistance in Melanocortin Circuits" International Congress of Neuroendocrinology. Pittsburgh June 2006.

"Leptin Sensitivity in Obesity and Cachexia. "University of Washington, Diabetes and Obesity Symposium. Seattle, July 2006.

"Melanocortin Circuits as Drug Targets". International Symposium on the Neurobiology of Obesity. Quebec, Canada, November 2005

"Diet induced obesity causes leptin resistance in melanocortin neurons". CSF Workshop: Peripheral-Central Interactions in the Control of Food Intake and Energy Balance. Ascona, Switzerland, September 2005

"Leptin effects on melanocortin circuits". Pennington Biomedical Research Center Scientific Symposium Physiological & Biological Properties of the AgRP-MCR Pathway. May 2005.

"Hypothalamic Melanocortin Neurons Integrate Signals of Energy State." Obesity: Molecular Physiology and Genetics of the Control of Body Weight. Keystone, January 2005.

"The adipostat: Neural sensing of energy status." US National Academy of Sciences/Indian Academy of Sciences Frontiers of Science. Food Intake and Energy Balance Symposium, January 2005

"The Pharmacology of Eating and Energy Utilization: Neurocircuitry and Effectors." Experimental Biology. Washington DC, April 2004.

"NPY neurons in the arcuate nucleus respond to gastric nutrient signals." 7th International NPY meeting, Coimbra Portugal, February 2004.

"Nutrient Signals Feed Back Through the Hypothalamus." Symposium on Neuronal and Humoral Regulation of the Hypothalamus and Pathogenesis of Obesity. NAASO Annual meeting Ft. Lauderdale, FL, October 2003.

"Electrophysiological studies of energy homeostasis." Copenhagen Obesity Symposium, Copenhagen, Denmark, September 2003.

"Hypothalamic melanocortin neurons integrate signals of energy state." European Journal of Pharmacology Spring Meeting, Utrecht, The Netherlands. June 2003.

"Leptin, Ghrelin and PYY3-36 act on Hypothalamic Circuits to alter Feeding." Pannam Institute, Copenhagen, Denmark 2002.

"Blaming the brain for obesity." Symposium. Society for Neuroscience. Orlando, FL, November 2002.

"Hypothalamic control of energy homeostasis: Arcuate circuits integrate central and peripheral signals of energy state." Neuroscience program, USC, Los Angeles, CA, September 2002.

"Electrophysiological actions of peripheral hormones on melanocortin neurons." 5th International Melanocortin meeting. Sunriver, Oregon. August 2002.

"Hypothalamic control of energy homeostasis: An electrophysiological perspective." Cajal Institute, Madrid, Spain, June 2002.

"Leptin, PYY3-36, and ghrelin act on melanocortin neurons." Eighth Benjamin Franklin / Lafeyette Seminar. La Napoule, France, June 2002.

"Leptin, ghrelin, insulin and glucose act on POMC neurons through an integrated network of arcuate neurons." SSIB Symposium on the developing story of glucoreceptor neurons. Philadelphia, PA June 2001.

"Physiologic characteristics of neuronal circuits underlying food intake." American Diabetes Association 61st Scientific Sessions. Symposium on Neural Regulation of Food Intake: Animals to Humans Philadelphia, PA. June 2001.

"Leptin increases the activity of arcuate POMC neurons by two mechanisms." Keystone Symposium "Obesity and the regulation of energy homeostasis." Taos, NM, February 2001.

"Neuroendocrine regulation of body fat: The adipostat." West Coast Endocrine Club, Carmel, CA, USA. February 2001.

"Leptin rapidly activates POMC neurons by two mechanisms." Neuroendocrinology Grand Rounds, Beth Israel Deaconess Hospital, Harvard Medical School, Boston, MA, USA. October 2000.

"Dual actions of leptin on POMC and NPY neurons in the arcuate." Ares-Serono 4th International workshop on developmental endocrinology. Cambridge, UK, September 2000.

"Actions of neuropeptides and leptin on energy homeostasis." FASEB meeting. San Diego, CA, USA, April 2000.

"Evidence of a cellular basis for the adipostat within parvocellular neurons of the paraventricular nucleus of the hypothalamus." Closing talk. 5th International NPY meeting. Grand Cayman, BWI, April 1999.

APPENDIX B

Contrave

Contrave is a fixed dose combination of low-dose naltrexone SR and bupropion SR. In our Contrave clinical trials to date, we have used an IR formulation of naltrexone. Commencing with our planned Phase III trials, naltrexone will be delivered through our proprietary SR formulation in order to improve its tolerability. We have developed and are using an SR formulation of bupropion.

Contrave Clinical Results

Phase II Clinical Trial. We initiated clinical testing of Contrave with a Phase II clinical trial in 2004. This trial enrolled 238 patients at eight U.S. clinical trial sites to evaluate the safety and efficacy of the Contrave combination. Patients accepted for the trial had a BMI in the range of 30 to 40, were non-smokers and did not have diabetes or other significant medical complications. On average, patients enrolled in this trial weighed approximately 95 kilograms, or 209 pounds, at the beginning of the trial, or baseline. Patients were randomly placed into one of four treatment groups:

- combination therapy, which consisted of 50mg naltrexone IR plus 300mg bupropion SR;
- bupropion monotherapy, which consisted of 300mg bupropion SR plus placebo;
- naltrexone monotherapy, which consisted of 50mg naltrexone IR plus placebo; and
- placebo, which consisted of two placebo pills.

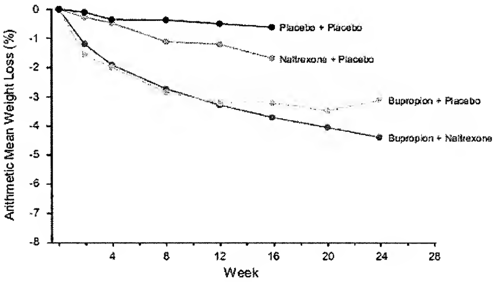
The primary endpoint for this trial was percent change in body weight measured 16 weeks after the start of treatment, with secondary endpoints that included the change in body weight 24 weeks after the start of treatment, and response rates based on the percentage of patients who lost at least 5% and 10% of their baseline weight 16 and 24 weeks after the start of treatment. The outcomes for patients receiving the combination regimen were compared to each individual monotherapy and placebo. We also monitored the safety and tolerability of Contrave in this trial. The statistical analysis plans for the first Phase II clinical trials for Contrave specified the use of an adjusted least-squares mean methodology for analysis of the primary endpoints. Accordingly, we have reported our results for these trials using this methodology. Least-square means methodology is based on a linear regression technique applied by statisticians to clinical trial data. We note that graphs that show weight loss over time for each treatment group in our trials utilize arithmetic mean data, because we believe this is the typical methodology used to present this type of chronological data.

On an intent-to-treat basis, which includes all randomized patients who recorded at least one post-baseline body weight measurement, Contrave demonstrated in this trial mean weight loss of 4.0% of baseline body weight at 16 weeks, compared to 3.6% for bupropion alone, 2.0% for

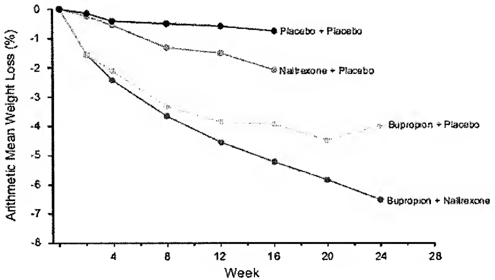
naltrexone alone and 1.0% for placebo. One important observation in this trial was that the benefit of adding naltrexone became more apparent over time, as weight loss curves for the combination therapy group gradually diverged from the bupropion monotherapy group. Accordingly, by 24 weeks, Contrave showed 5.2% weight loss on an intent-to-treat basis, compared to 4.0% for bupropion alone. When this analysis is restricted to those patients who completed 16 weeks of treatment, Contrave demonstrated mean weight loss of 4.8% of baseline body weight, compared to 3.9 % for bupropion alone, 2.3% for naltrexone alone and 1.0% for placebo. By 24 weeks, Contrave showed 6.8% weight loss among completers, compared to 4.5% for bupropion alone.

Weight loss, plotted over time on both an intent-to-treat basis as well as for completers, is as follows:

Contrave Phase II Mean Weight Loss through 24 Weeks
Intent-to-Treat Population



Contrave Phase II Mean Weight Loss through 24 Weeks Completer Population



Phase IIb Clinical Trial. Based on the results of our initial Phase II trial for Contrave, we concluded that Contrave showed sufficient efficacy and an acceptable safety and tolerability profile to warrant continued development. In July 2005, we proceeded to study Contrave in a larger Phase IIb trial exploring a higher dose of bupropion and lower doses of naltrexone at eight clinical sites in the United States. This trial was submitted to the FDA as a Phase II trial. However, because we believed that the results from this clinical trial provide sufficient evidence of the superiority of the combination drug therapy to the individual monotherapies and placebo in the treatment of obesity, we have characterized this study as a Phase IIb trial. In recent correspondence with the FDA, the agency has indicated that the results from this trial enable future pivotal studies to be conducted based on a comparison of the combination therapy to placebo only.

The Phase IIb trial was designed to evaluate patients for 24 weeks under double-blind conditions. Patients accepted for the trial had a BMI in the range of 30 to 40, were non-smokers and did not have diabetes or other significant medical complications. On average, patients enrolled in this trial weighed approximately 95 kilograms, or 209 pounds, at baseline. Patients were initially randomly placed into one of five treatment groups:

- 48mg naltrexone IR plus 400mg bupropion SR;
- 16mg naltrexone IR plus 400mg bupropion SR;
- bupropion monotherapy, which consisted of 400mg bupropion SR plus placebo;
- naltrexone monotherapy, which consisted of 48mg naltrexone IR plus placebo; and
- placebo, which consisted of two placebo pills.

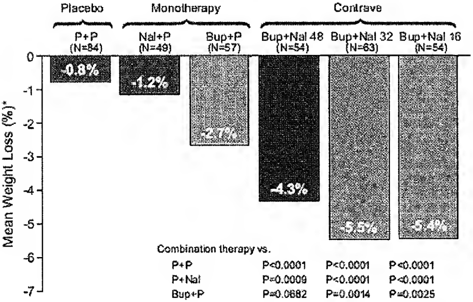
The primary endpoint for this trial was percent change in body weight measured 24 weeks after the start of treatment, with secondary endpoints that included the percentage of patients who lost at least 5% and 10% of their baseline weight 24 weeks after the start of treatment. The outcomes for patients receiving the combination regimen were compared to each individual monotherapy and placebo. We also monitored the safety and tolerability of Contrave in this trial. For the Contrave Phase IIb clinical trial, the statistical analysis plan specified the use of an unadjusted least-squares mean methodology for analysis of the primary endpoint. Accordingly, we have reported our results for this trial using this methodology.

In addition, we added a second set of patients randomized either to 32mg naltrexone plus 400mg bupropion or a double placebo. While these patients were enrolled subsequent to the initial group of patients, the clinical sites, investigators and study protocols remained constant. The statistical analysis plan submitted to the FDA included specifications for a pooled analysis of both groups of patients. In total, 361 patients between the two sets were randomized and had at least one post-baseline body measurement. These patients represent the intent-to-treat population.

After 24 weeks, patients initially randomized to placebo or naltrexone monotherapy were crossed over to naltrexone 32mg plus bupropion 400mg therapy; all other patients continued to receive their originally assigned treatment for an additional 24 weeks of open-label treatment. Data for the crossover group were segregated and were not considered for the efficacy analysis presented below.

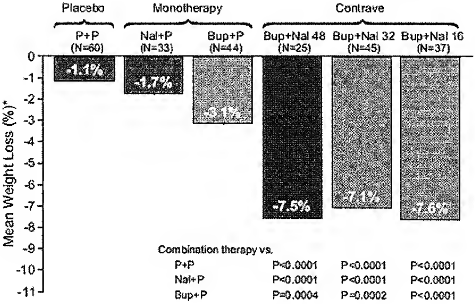
We believe the 24 week data show significant advantages of Contrave therapy for the treatment of obesity compared to the efficacy demonstrated by the respective monotherapies and placebo. The 24 week results are depicted graphically for the intent-to-treat and completer populations as follows:

Contrave Phase IIb Mean Weight Loss at 24 Weeks Intent-to-Treat Population



* Calculated on the basis of unadjusted least-squares mean methodology.

Contrave Phase IIb Mean Weight Loss at 24 Weeks Completer Population



* Calculated on the basis of unadjusted least-squares mean methodology.

"N" indicates the number of patients in the treatment group. P-values indicate the likelihood that clinical trial results were due to random statistical fluctuations rather than true cause and effect. The lower the p-value, the more likely there is a true cause-and-effect relationship. Typically, the FDA requires a p-value of less than 0.05 to establish the statistical significance of a clinical trial.

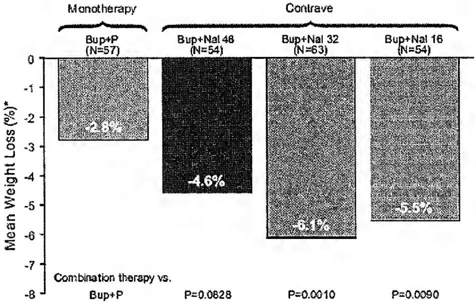
As noted, the p-values were statistically significant among all comparisons (intent-to-treat and completers) with the exception of a single comparison for the intent-to-treat population between 48mg naltrexone IR plus 400mg bupropion SR compared to 400 mg bupropion SR alone where the p-value was 0.068.

With regard to the 5% and 10% categorical response rates, patients in the three Contrave combination therapy groups performed substantially better than monotherapy as well as placebo patients. For the intent-to-treat population at 24 weeks, between 39% and 52% of patients on the three dosages of Contrave lost at least 5% of their body weight, compared to 26% for bupropion alone, 10% for naltrexone alone and 15% for placebo. Between 15% and 19% of patients on the three dosages of Contrave in the intent-to-treat group lost at least 10% of their body weight, compared to 7% for bupropion alone, 2% for naltrexone alone and 2% for placebo. For the completer population, between 64% and 70% of patients on the three dosages of Contrave lost at least 5% of their body weight, compared to 32% for bupropion alone, 15% for naltrexone alone and 20% for placebo. Between 24% and 32% of patients on the three dosages of Contrave in the completer group lost at least 10% of their body weight, compared to 9% for bupropion alone, 3% for naltrexone alone and 3% for placebo.

Discontinuation of study drug due to an adverse event generally occurred early in treatment. As a result, in the intent-to-treat analysis, the naltrexone 48mg IR plus bupropion 400mg bupropion SR treatment appears somewhat less effective than other Contrave dosages. Use of the last-observation-carried-forward, or LOCF, method implies that data for patients who drop out of the study prior to completion are carried forward in the analysis. Thus, limited weight loss observed early in the course of treatment in patients who discontinued treatment early averages down the efficacy observed in patients who remained on therapy for longer periods of time. This effect is illustrated when comparing the intent-to-treat results to the completers' analysis.

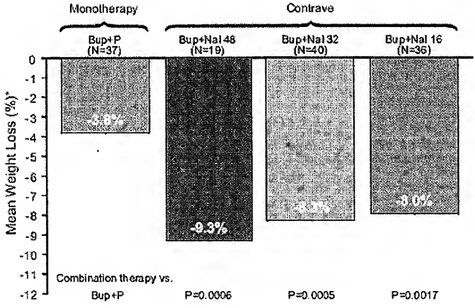
As noted, weight loss at 24 weeks was the primary endpoint for this trial. However, the protocol permitted study participants to continue on Contrave or bupropion for an additional 24 week period. The study is ongoing and 48 week data is not yet available. Data through 36 weeks of treatment indicates that subjects, on average, continued to lose weight in the interval from weeks 24 to 36. For the intent-to-treat and completer populations, the results were as follows:

Contrave Phase IIb Mean Weight Loss at 36 Weeks
Intent-to- Treat Population



* Calculated on the basis of unadjusted least-squares mean methodology.

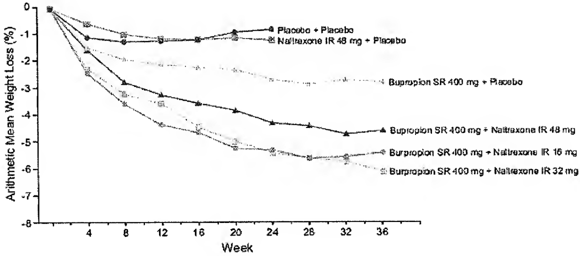
Contrave Phase IIb Mean Weight Loss at 36 Weeks Completer Population



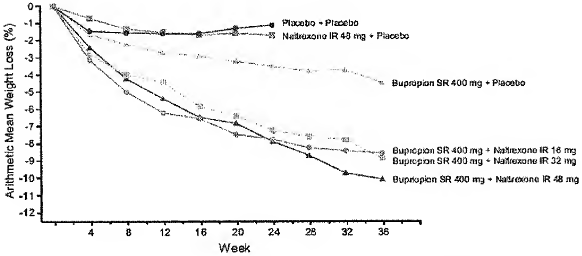
* Calculated on the basis of unadjusted least-squares mean methodology.

As noted, the p-values were statistically significant among all comparisons (intent-to-treat and completers) with the exception of a single comparison for the intent-to-treat population between 48mg naltrexone IR plus 400mg bupropion SR compared to 400 mg bupropion SR alone where the p-value was 0.083. Weight loss through 36 weeks, plotted for the intent-to-treat and completer populations, is as follows:

Contrave Phase IIb Mean Weight Loss Over 36 Weeks
Intent-to- Treat Population



Contrave Phase IIb Mean Weight Loss Over 36 Weeks
Completer Population



As these results imply, most patients continued to lose weight between 24 weeks and 36 weeks.